HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BYETTA safely and effectively. See full prescribing information for BYETTA.
BYETTA® (exenatide) Injection
Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Indications and Usage Monotherapy and Combination Therapy (1.1)	10/2009
Important Limitations of Use History of Pancreatitis (1.2)	10/2009
Warnings and Precautions Pancreatitis (5.1) Renal Impairment (5.3) Macrovascular Outcomes (5.7)	10/2009

INDICATIONS AND USAGE

BYETTA is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use
- BYETTA is not a substitute for insulin. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (1.2).
- The concurrent use of BYETTA with insulin has not been studied and cannot be recommended (1.2).
- BYETTA has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (1.2).

DOSAGE AND ADMINISTRATION
- Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart) (2.1).
- Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response (2.1).

DOSAGE FORMS AND STRENGTHS

BYETTA is supplied as 250 mcg/mL exenatide in:
- 5 mcg per dose, 60 doses, 1.2 mL prefilled pen
- 10 mcg per dose, 60 doses, 2.4 mL prefilled pen

CONTRAINDICATIONS
- History of severe hypersensitivity to exenatide or any product components (4.1).

WARNINGS AND PRECAUTIONS
- Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. *Discontinue BYETTA promptly. BYETTA should not be restarted.* Consider other antidiabetic therapies in patients with a history of pancreatitis (5.1).
- Hypoglycemia: Increased risk when BYETTA is used in combination with a sulfonylurea. Consider reducing the sulfonylurea dose (5.2).
- Renal Impairment: Postmarketing reports, sometimes requiring hemodialysis and kidney transplantation. BYETTA should *not* be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating BYETTA or escalating the dose of BYETTA in patients with moderate renal failure (5.3).
- Severe Gastrointestinal Disease: Use of BYETTA is not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis) (5.4).
- Hypersensitivity: Postmarketing reports of hypersensitivity reactions (e.g. anaphylaxis and angioedema). The patient should discontinue BYETTA and other suspect medications and promptly seek medical advice (5.6).
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug (5.7).

ADVERSE REACTIONS
- Most common (≥5%) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia. Nausea usually decreases over time (5.2; 6).
- Postmarketing reports of increased international normalized ratio (INR) with concomitant use of warfarin, sometimes with bleeding (6.2).

To report SUSPECTED ADVERSE REACTIONS contact Amylin Pharmaceuticals, Inc. and Eli Lilly and Company at 1-800-868-1190 and www.byetta.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS
- Warfarin: Postmarketing reports of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation or alteration of BYETTA therapy (7.2).

USE IN SPECIFIC POPULATIONS
- Pregnancy: Based on animal data, BYETTA may cause fetal harm. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To report drug exposure during pregnancy call 1-800-633-9081 (8.1).
- Nursing Mothers: Caution should be exercised when BYETTA is administered to a nursing woman (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Exhibit A

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Type 2 Diabetes Mellitus

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.2 Important Limitations of Use

BYETTA is not a substitute for insulin. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYETTA with insulin has not been studied and cannot be recommended.

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYETTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

BYETTA should be initiated at 5 mcg administered twice daily at any time within the 60-minute period before the morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). BYETTA should not be administered after a meal. Based on clinical response, the dose of BYETTA can be increased to 10 mcg twice daily after 1 month of therapy. Initiation with 5 mcg reduces the incidence and severity of gastrointestinal side effects. Each dose should be administered as a subcutaneous (SC) injection in the thigh, abdomen, or upper arm. No data are available on the safety or efficacy of intravenous or intramuscular injection of BYETTA.

Use BYETTA only if it is clear, colorless and contains no particles.

3 DOSAGE FORMS AND STRENGTHS

BYETTA is supplied as a sterile solution for subcutaneous injection containing 250 mcg/mL exenatide in the following packages:

- 5 mcg per dose, 60 doses, 1.2 mL prefilled pen
- 10 mcg per dose, 60 doses, 2.4 mL prefilled pen

4 CONTRAINDICATIONS

4.1 Hypersensitivity

BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Pancreatitis

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis.

5.2 Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea (hypoglycemia can also occur when other antidiabetic agents are used in combination with a sulfonylurea). Therefore, patients receiving BYETTA and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia. It is also possible that the use of BYETTA with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

For additional information on glucose dependent effects see *Mechanism of Action (12.1).*

5.3 Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation *[see Use in Specific Populations (8.6)]*. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients

receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

5.4 Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

5.5 Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small proportion of patients, the formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered *[see Adverse Reactions (6.1)]*.

5.6 Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and other suspect medications and promptly seek medical advice *[see Adverse Reactions (6.2)]*.

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypoglycemia

Table 1 summarizes the incidence and rate of hypoglycemia with BYETTA in five placebo-controlled clinical trials.

Table 1: Incidence (%) and Rate of Hypoglycemia When BYETTA was Used as Monotherapy or With Concomitant Antidiabetic Therapy in Five Placebo-Controlled Clinical Trials*

		BYETTA	
	Placebo twice daily	**5 mcg twice daily**	**10 mcg twice daily**
Monotherapy (24 Weeks)			
N	77	77	78
% Overall	1.3%	5.2%	3.8%
Rate (episodes/patient-year)	0.03	0.21	0.52
% Severe	0.0%	0.0%	0.0%
With Metformin (30 Weeks)			
N	113	110	113
% Overall	5.3%	4.5%	5.3%
Rate (episodes/patient-year)	0.12	0.13	0.12
% Severe	0.0%	0.0%	0.0%
With a Sulfonylurea (30 Weeks)			
N	123	125	129
% Overall	3.3%	14.4%	35.7%
Rate (episodes/patient-year)	0.07	0.64	1.61
% Severe	0.0%	0.0%	0.0%
With Metformin and a Sulfonylurea (30 Weeks)			
N	247	245	241
% Overall	12.6%	19.2%	27.8%
Rate (episodes/patient-year)	0.58	0.78	1.71
% Severe	0.0%	0.4%	0.0%
With a Thiazolidinedione (16 Weeks)			
N	112	Dose not studied	121
% Overall	7.1%	Dose not studied	10.7%
Rate (episodes/patient-years)	0.56	Dose not studied	0.98
% Severe	0.0%	Dose not studied	0.0%

* For the 30-week trials, a hypoglycemia episode was recorded if the patient reported symptoms consistent with hypoglycemia and was recorded as severe if the subject required the assistance of another person to treat the event. For the other trials, a hypoglycemic episode was recorded if a patient reported signs or symptoms of hypoglycemia or had a blood glucose value consistent with hypoglycemia regardless of associated symptoms or treatment and was recorded as severe if the subject required the assistance of another person to treat the event. The requirement for assistance had to be accompanied by a blood glucose measurement of <50 mg/dL or prompt recovery after administration of oral carbohydrate.

N = The number of Intent-to-Treat subjects in each treatment group.

Immunogenicity

In the 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, 38% of patients had low titer antibodies to exenatide at 30 weeks. For this group, the level of glycemic control (hemoglobin A1c [HbA_{1c}]) was generally comparable to that observed in those without antibody titers. An additional 6% of patients had higher titer antibodies at 30 weeks. In about half of this 6% (3% of the total patients given BYETTA in the 30-week controlled studies), the glycemic response to BYETTA was attenuated; the remainder had a glycemic response comparable to that of patients without antibodies.

In the 16-week trial of BYETTA add-on to thiazolidinediones, with or without metformin, 9% of patients had higher titer antibodies at 16 weeks. In the 24-week trial of BYETTA used as monotherapy, 3% of patients had higher titer antibodies at 24 weeks. Compared with patients who did not develop antibodies to BYETTA, on average the glycemic response in patients with higher titer antibodies was attenuated *[see Warnings and Precautions (5.5)]*.

Other Adverse Reactions

Monotherapy

For the 24-week placebo-controlled study of BYETTA used as a monotherapy, Table 2 summarizes adverse reactions (excluding hypoglycemia) occurring with an incidence ≥2% and occurring more frequently in BYETTA-treated patients compared with placebo-treated patients.

Table 2: Treatment-Emergent Adverse Reactions ≥2% Incidence With BYETTA Used as Monotherapy (Excluding Hypoglycemia)*

Monotherapy	Placebo BID N = 77 %	All BYETTA BID N = 155 %
Nausea	0	8
Vomiting	0	4
Dyspepsia	0	3

* In a 24-week placebo-controlled trial.
BID = twice daily.

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite, diarrhea, and dizziness. The most frequently reported adverse reaction associated with BYETTA, nausea, occurred in a dose-dependent fashion.

Two of the 155 patients treated with BYETTA withdrew due to adverse reactions of headache and nausea. No placebo-treated patients withdrew due to adverse reactions.

Combination Therapy

Add-on to metformin and/or sulfonylurea

In the three 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, adverse reactions (excluding hypoglycemia) with an incidence ≥2% and occurring more frequently in BYETTA-treated patients compared with placebo-treated patients *[see Warnings and Precautions (5.2)]* are summarized in Table 3.

Table 3: Treatment-Emergent Adverse Reactions ≥2% Incidence and Greater Incidence With BYETTA Treatment Used With Metformin and/or a Sulfonylurea (Excluding Hypoglycemia)*

	Placebo BID N = 483 %	All BYETTA BID N = 963 %
Nausea	18	44
Vomiting	4	13
Diarrhea	6	13
Feeling Jittery	4	9
Dizziness	6	9
Headache	6	9
Dyspepsia	3	6
Asthenia	2	4
Gastroesophageal Reflux Disease	1	3
Hyperhidrosis	1	3

* In three 30-week placebo-controlled clinical trials.
BID = twice daily.

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Nausea was the most frequently reported adverse reaction and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Patients in the long-term uncontrolled open-label extension studies at 52 weeks reported no new types of adverse reactions than those observed in the 30-week controlled trials.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients, <1% withdrew due to nausea and none due to vomiting.

Add-on to thiazolidinedione with or without metformin

For the 16-week placebo-controlled study of BYETTA add-on to a thiazolidinedione, with or without metformin, Table 4 summarizes the adverse reactions (excluding hypoglycemia) with an incidence of ≥2% and occurring more frequently in BYETTA-treated patients compared with placebo-treated patients.

Table 4: Treatment-Emergent Adverse Reactions ≥2% Incidence With BYETTA Used With a Thiazolidinedione, With or Without Metformin (Excluding Hypoglycemia)*

With a TZD or TZD/MET	Placebo N = 112 %	All BYETTA BID N = 121 %
Nausea	15	40
Vomiting	1	13
Dyspepsia	1	7
Diarrhea	3	6
Gastroesophageal Reflux Disease	0	3

* In a 16-week placebo-controlled clinical trial.
BID = twice daily.

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Chills (n = 4) and injection-site reactions (n = 2) occurred only in BYETTA-treated patients. The two patients who reported an injection-site reaction had high titers of antibodies to exenatide. Two serious adverse events (chest pain and chronic hypersensitivity pneumonitis) were reported in the BYETTA arm. No serious adverse events were reported in the placebo arm.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients, <1% withdrew due to nausea.

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema, anaphylactic reaction *[see Warnings and Precautions (5.6)]*.

Drug Interactions: International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding *[see Drug Interactions (7.2)]*.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Limitations of Use (1.2) and Warnings and Precautions (5.1)]*.

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring

hemodialysis), kidney transplant and kidney transplant dysfunction *[see Warnings and Precautions (5.3)]*.

Skin and Subcutaneous Tissue Disorders: alopecia

7 DRUG INTERACTIONS

7.1 Orally Administered Drugs

The effect of BYETTA to slow gastric emptying can reduce the extent and rate of absorption of orally administered drugs. BYETTA should be used with caution in patients receiving oral medications that have narrow therapeutic index or require rapid gastrointestinal absorption *[see Adverse Reactions (6.2)]*. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 hour before BYETTA injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when BYETTA is not administered *[see Clinical Pharmacology (12.3)]*.

7.2 Warfarin

There are postmarketing reports of increased INR sometimes associated with bleeding, with concomitant use of warfarin and BYETTA *[see Adverse Reactions (6.2)]*. In a drug interaction study, BYETTA did not have a significant effect on INR *[see Clinical Pharmacology (12.3)]*. In patients taking warfarin, prothrombin time should be monitored more frequently after initiation or alteration of BYETTA therapy. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYETTA use in pregnant women. In animal studies, exenatide caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Female mice given SC doses of 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC *[see Nonclinical Toxicology (13.3)]*.

In developmental toxicity studies, pregnant animals received exenatide subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given SC doses of 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC. Moreover, fetuses from pregnant mice given SC doses of 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC *[see Nonclinical Toxicology (13.3)]*.

Lactating mice given SC doses of 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC *[see Nonclinical Toxicology (13.3)]*.

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

8.3 Nursing Mothers

It is not known whether exenatide is excreted in human milk. However, exenatide is present at low concentrations (less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing) in the milk of lactating mice. Many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from exenatide, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account these potential risks against the glycemic benefits to the lactating woman. Caution should be exercised when BYETTA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BYETTA have not been established in pediatric patients.

8.5 Geriatric Use

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide *[see Clinical Pharmacology (12.3)]*. BYETTA was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function.

8.6 Renal Impairment

BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 mL/min) and should be used with caution in patients with renal transplantation. No dosage adjustment of BYETTA is required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In a clinical study of BYETTA, three patients with type 2 diabetes each experienced a single overdose of 100 mcg SC (10 times the maximum recommended dose). Effects of the overdoses included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. One of the three patients experienced severe hypoglycemia requiring parenteral glucose administration. The three patients recovered without complication. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

BYETTA (exenatide) is a synthetic peptide that was originally identified in the lizard *Heloderma suspectum*. Exenatide differs in chemical structure and pharmacological action from insulin, sulfonylureas (including D-phenylalanine derivatives and meglitinides), biguanides, thiazolidinediones, alpha-glucosidase inhibitors, amylinomimetics and dipeptidyl peptidase-4 inhibitors.

Exenatide is a 39-amino acid peptide amide. Exenatide has the empirical formula $C_{184}H_{282}N_{50}O_{60}S$ and molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu -Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

BYETTA is supplied for SC injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen-injector (pen). Each milliliter (mL) contains 250 micrograms (mcg) synthetic exenatide, 2.2 mg metacresol as an antimicrobial preservative, mannitol as a tonicity-adjusting agent, and glacial acetic acid and sodium acetate trihydrate in water for

injection as a buffering solution at pH 4.5. Two prefilled pens are available to deliver unit doses of 5 mcg or 10 mcg. Each prefilled pen will deliver 60 doses to provide for 30 days of twice daily administration (BID).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. BYETTA is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide has been shown to bind and activate the human GLP-1 receptor in vitro. This leads to an increase in both glucose-dependent synthesis of insulin, and in vivo secretion of insulin from pancreatic beta cells, by mechanisms involving cyclic AMP and/or other intracellular signaling pathways. Exenatide promotes insulin release from pancreatic beta cells in the presence of elevated glucose concentrations.

BYETTA improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through the actions described below.

Glucose-dependent insulin secretion: BYETTA has acute effects on pancreatic beta-cell responsiveness to glucose leading to insulin release predominantly in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. However, BYETTA does not impair the normal glucagon response to hypoglycemia.

First-phase insulin response: In healthy individuals, robust insulin secretion occurs during the first 10 minutes following intravenous (IV) glucose administration. This secretion, known as the "first-phase insulin response," is characteristically absent in patients with type 2 diabetes. The loss of the first-phase insulin response is an early beta-cell defect in type 2 diabetes. Administration of BYETTA at therapeutic plasma concentrations restored first-phase insulin response to an IV bolus of glucose in patients with type 2 diabetes (Figure 1). Both first-phase insulin secretion and second-phase insulin secretion were significantly increased in patients with type 2 diabetes treated with BYETTA compared with saline ($p < 0.001$ for both).

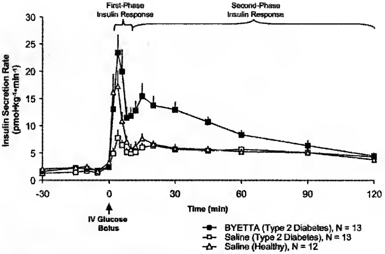


Figure 1: Mean (+SEM) Insulin Secretion Rate During Infusion of BYETTA or Saline in Patients With Type 2 Diabetes and During Infusion of Saline in Healthy Subjects

Glucagon secretion: In patients with type 2 diabetes, BYETTA moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand.

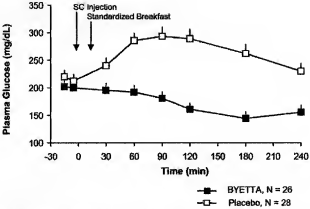
Gastric emptying: BYETTA slows gastric emptying, thereby reducing the rate at which meal-derived glucose appears in the circulation.

Food intake: In both animals and humans, administration of exenatide has been shown to reduce food intake.

12.2 Pharmacodynamics

Postprandial Glucose

In patients with type 2 diabetes, BYETTA reduces postprandial plasma glucose concentrations (Figure 2).

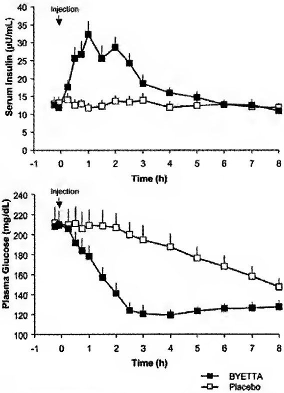


[a]Mean dose (7.8 mcg based on body weight) was administered by subcutaneous (SC) injection.

Figure 2: Mean (+SEM) Postprandial Plasma Glucose Concentrations on Day 1 of BYETTA[a] Treatment in Patients With Type 2 Diabetes Treated With Metformin, a Sulfonylurea, or Both (N = 54)

Fasting Glucose

In a single-dose crossover study in patients with type 2 diabetes and fasting hyperglycemia, immediate insulin release followed injection of BYETTA. Plasma glucose concentrations were significantly reduced with BYETTA compared with placebo (Figure 3).



[a] BYETTA administration was based on body weight at baseline, mean dose was 9.1 mcg.

Figure 3: Mean (+SEM) Serum Insulin and Plasma Glucose Concentrations Following a One-Time Injection of BYETTA[a] or Placebo in Fasting Patients With Type 2 Diabetes (N = 12)

12.3 Pharmacokinetics

Absorption

Following SC administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2.1 h. The mean peak exenatide concentration (C_{max}) was 211 pg/mL and overall mean area under the time-concentration curve ($AUC_{0\text{-}inf}$) was 1036 pg•h/mL following SC administration of a 10-mcg dose of BYETTA. Exenatide exposure (AUC) increased proportionally over the therapeutic dose range of 5 mcg to 10 mcg. The C_{max} values increased less than proportionally over the same range. Similar exposure is achieved with SC administration of BYETTA in the abdomen, thigh, or upper arm.

Distribution

The mean apparent volume of distribution of exenatide following SC administration of a single dose of BYETTA is 28.3 L.

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/h and the mean terminal half-life is 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 h post-dose.

Drug Interactions

Acetaminophen

When 1000 mg acetaminophen elixir was given with 10 mcg BYETTA (0 h) and 1 hour, 2 hours, and 4 hours after BYETTA injection, acetaminophen AUCs were decreased by 21%, 23%, 24%, and 14%, respectively; C_{max} was decreased by 37%, 56%, 54%, and 41%, respectively; T_{max} was increased from 0.6 hour in the control period to 0.9 hour, 4.2 hours, 3.3 hours, and 1.6 hours, respectively. Acetaminophen AUC, C_{max} and T_{max} were not significantly changed when acetaminophen was given 1 hour before BYETTA injection.

Digoxin

Administration of repeated doses of BYETTA (10 mcg BID) 30 minutes before oral digoxin (0.25 mg QD) decreased the C_{max} of digoxin by 17% and delayed the T_{max} of digoxin by approximately 2.5 hours; however, the overall steady-state pharmacokinetic exposure (e.g., AUC) of digoxin was not changed.

Lovastatin

Administration of BYETTA (10 mcg BID) 30 minutes before a single oral dose of lovastatin (40 mg) decreased the AUC and C_{max} of lovastatin by approximately 40% and 28%, respectively, and delayed the T_{max} by about 4 hours compared with lovastatin administered alone. In the 30-week controlled clinical trials of BYETTA, the use of BYETTA in patients already receiving HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles compared to baseline.

Lisinopril

In patients with mild to moderate hypertension stabilized on lisinopril (5 to 20 mg/day), BYETTA (10 mcg BID) did not alter steady-state C_{max} or AUC of lisinopril. Lisinopril steady-state T_{max} was delayed by 2 hours. There were no changes in 24-h mean systolic and diastolic blood pressure.

Oral Contraceptives

The effect of BYETTA (10 mcg BID) on single and on multiple doses of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) was studied in healthy female subjects. Repeated daily doses of the oral contraceptive (OC) given 30 minutes after BYETTA administration decreased the C_{max} of ethinyl estradiol and levonorgestrel by 45% and 27%, respectively and delayed the T_{max} of ethinyl estradiol and levonorgestrel by 3.0 hours and 3.5 hours, respectively, as compared to the oral contraceptive administered alone. Administration of repeated daily doses of the OC one hour prior to BYETTA administration decreased the mean C_{max} of ethinyl estradiol by 15% but the mean C_{max} of levonorgestrel was not significantly changed as compared to when the OC was given alone. BYETTA did not alter the mean trough concentrations of levonorgestrel after repeated daily dosing of the oral contraceptive for both regimens. However, the mean trough concentration of ethinyl estradiol was increased by 20% when the OC was administered 30 minutes after BYETTA administration injection as compared to when the OC was given alone. The effect of BYETTA on OC pharmacokinetics is confounded by the possible food effect on OC in this study. Therefore, OC products should be administered at least one hour prior to BYETTA injection.

Warfarin

Administration of warfarin (25 mg) 35 minutes after repeated doses of BYETTA (5 mcg BID on days 1-2 and 10 mcg BID on days 3-9) in healthy volunteers delayed warfarin T_{max} by approximately 2 hours. No clinically relevant effects on C_{max} or AUC of S- and R-enantiomers of warfarin were observed. BYETTA did not significantly alter the pharmacodynamic properties (e.g., international normalized ratio) of warfarin *[see Drug Interactions (7.2)]*.

Specific Populations

Renal Impairment

Pharmacokinetics of exenatide was studied in subjects with normal, mild, or moderate renal impairment and subjects with end stage renal disease. In subjects with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), exenatide exposure was similar to that of subjects with normal renal function. However, in subjects with end-stage renal disease receiving dialysis, mean exenatide exposure increased by 3.37-fold compared to that of subjects with normal renal function. *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment *[see Use in Specific Populations (8.7)]*.

Age

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide *[see Use in Specific Population (8.5)]*.

Gender

Population pharmacokinetic analysis of male and female patients suggests that gender does not influence the distribution and elimination of exenatide.

Race

Population pharmacokinetic analysis of samples from Caucasian, Hispanic, Asian, and Black patients suggests that race has no significant influence on the pharmacokinetics of exenatide.

Body Mass Index

Population pharmacokinetic analysis of patients with body mass indices (BMI) ≥30 kg/m^2 and <30 kg/m^2 suggests that BMI has no significant effect on the pharmacokinetics of exenatide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female rats at doses of 18, 70, or 250 mcg/kg/day administered by bolus SC injection. Benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups with systemic exposures of 5, 22, and 130 times, respectively, the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on plasma area under the curve (AUC).

In a 104-week carcinogenicity study in mice at doses of 18, 70, or 250 mcg/kg/day administered by bolus SC injection, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 95 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

Exenatide was not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells. Exenatide was negative in the in vivo mouse micronucleus assay.

In mouse fertility studies with SC doses of 6, 68 or 760 mcg/kg/day, males were treated for 4 weeks prior to and throughout mating, and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 760 mcg/kg/day, a systemic exposure 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

13.3 Reproductive and Developmental Toxicology

In female mice given SC doses of 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7, there were no adverse fetal effects at doses up to 760 mcg/kg/day, systemic exposures up to 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In pregnant mice given SC doses of 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 (organogenesis), cleft palate (some with holes) and irregular fetal skeletal ossification of rib and skull bones were observed at 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In pregnant rabbits given SC doses of 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 (organogenesis), irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a systemic exposure 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In pregnant mice given SC doses of 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths was observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

14 CLINICAL STUDIES

BYETTA has been studied as monotherapy and in combination with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione.

14.1 Monotherapy

In a randomized, double-blind, placebo-controlled trial of 24 weeks duration, BYETTA 5 mcg BID (n = 77), BYETTA 10 mcg BID (n = 78), or placebo BID (n = 77) was used as monotherapy in patients with entry HbA_{1c} ranging from 6.5-10%. All patients assigned to BYETTA initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients either continued to receive BYETTA 5 mcg BID or had their dose increased to 10 mcg BID. Patients assigned to placebo received placebo BID throughout the trial. BYETTA or placebo was injected subcutaneously before the morning and evening meals. The majority of patients (68%) were Caucasian, 26% were West Asian, 3% were Hispanic, 3% were Black, and 0.4% were East Asian.

The primary endpoint was the change in HbA_{1c} from baseline to Week 24 (or the last value at time of early discontinuation). Compared to placebo, BYETTA 5 mcg BID and 10 mcg BID resulted in statistically significant reductions in HbA_{1c} from baseline at Week 24 (Table 5).

Table 5: Results of 24-Week Placebo-Controlled Trial of BYETTA Used as Monotherapy

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
Intent-to-Treat Population (N)	77	77	78
HbA_{1c} (%), Mean			
Baseline	7.8	7.9	7.8
Change at Week 24†	-0.2	-0.7	-0.9
Difference from placebo†(95% CI)		-0.5 [-0.9, -0.2]‡	-0.7 [-1.0, -0.3]‡
Proportion Achieving HbA_{1c} <7%	38%	48%	53%
Body Weight (kg), Mean			
Baseline	86.1	85.1	86.2
Change at Week 24†	-1.5	-2.7	-2.9
Difference from placebo†(95% CI)		-1.3 [-2.3, -0.2]	-1.5 [-2.5, -0.4]
Fasting Serum Glucose§ (mg/dL), Mean			
Baseline	159	166	155
Change at Week 24†	-5	-17	-19
Difference from placebo† (95% CI)		-12 [-23.2, -1.3]	-14 [-24.5, -2.5]

* BYETTA 5 mcg twice daily (BID) for 1 month followed by 10 mcg BID for 5 months before the morning and evening meals.

† Least squares means are adjusted for screening HbA_{1c} strata and baseline value of the dependent variable.

‡ $p < 0.01$, treatment vs. placebo.

§ Measured using the hexokinase-based glucose method.

BID = twice daily.

On average, there were no adverse effects of exenatide on blood pressure or lipids.

14.2 Combination Therapy

Three 30-week, double-blind, placebo-controlled trials were conducted to evaluate the safety and efficacy of BYETTA in patients with type 2 diabetes whose glycemic control was inadequate with metformin alone, a sulfonylurea alone, or metformin in combination with a sulfonylurea. In addition, a 16-week, placebo-controlled trial was conducted where BYETTA was added to existing thiazolidinedione (pioglitazone or rosiglitazone) treatment, with or without metformin, in patients with type 2 diabetes with inadequate glycemic control.

In the 30-week trials, after a 4-week placebo lead-in period, patients were randomly assigned to receive BYETTA 5 mcg BID, BYETTA 10 mcg BID, or placebo BID before the morning and evening meals, in addition to their existing oral antidiabetic agent. All patients assigned to BYETTA initially received 5 mcg BID for 4 weeks. After 4 weeks, those patients either continued to receive BYETTA 5 mcg BID or had their dose increased to 10 mcg BID. Patients assigned to placebo received placebo BID throughout the study. A total of 1446 patients were randomized in the three 30-week trials: 991 (69%) were Caucasian, 224 (16%) were Hispanic,

and 174 (12%) were Black. Mean HbA_{1c} values at baseline for the trials ranged from 8.2% to 8.7%.

In the placebo-controlled trial of 16 weeks duration, BYETTA (n = 121) or placebo (n = 112) was added to existing thiazolidinedione (pioglitazone or rosiglitazone) treatment, with or without metformin. Randomization to BYETTA or placebo was stratified based on whether the patients were receiving metformin. BYETTA treatment was initiated at a dose of 5 mcg BID for 4 weeks then increased to 10 mcg BID for 12 more weeks. Patients assigned to placebo received placebo BID throughout the study. BYETTA or placebo was injected subcutaneously before the morning and evening meals. In this trial, 79% of patients were taking a thiazolidinedione and metformin and 21% were taking a thiazolidinedione alone. The majority of patients (84%) were Caucasian, 8% were Hispanic and 3% were Black. The mean baseline HbA_{1c} values were 7.9% for BYETTA and placebo.

The primary endpoint in each study was the mean change in HbA_{1c} from baseline to study end (or early discontinuation). Table 6 summarizes the study results for the 30-week and 16-week clinical trials.

Table 6: Results of 30-Week and 16-Week Placebo-Controlled Trials of BYETTA Used in Combination with Oral Antidiabetic Agents

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
	In Combination With Metformin (30 Weeks)		
Intent-to-Treat Population (N)	113	110	113
HbA_{1c} (%), Mean			
Baseline	8.2	8.3	8.2
Change at Week 30†	-0.0	-0.5	-0.9
Difference from placebo† (95% CI)		-0.5 [-0.7, -0.2]‡	-0.9 [-1.1, -0.6]‡
Proportion Achieving HbA_{1c} <7%	12%	32%	40%
Body Weight (kg), Mean			
Baseline	99.9	100.0	100.9
Change at Week 30†	-0.2	-1.3	-2.6
Difference from placebo† (95% CI)		-1.1 [-2.2, -0.0]	-2.4 [-3.5, -1.3]
Fasting Plasma Glucose§ (mg/dL), Mean			
Baseline	169	176	168
Change at Week 30†	+14	-5	-10
Difference from placebo† (95% CI)		-20 [-32, -7]	-24 [-37, -12]
	In Combination With a Sulfonylurea (30 Weeks)		
Intent-to-Treat Population (N)	123	125	129
HbA_{1c} (%), Mean			
Baseline	8.7	8.5	8.6
Change at Week 30†	+0.1	-0.5	-0.9
Difference from placebo† (95% CI)		-0.6 [-0.9, -0.3]‡	-1.0 [-1.3, -0.7]‡
Proportion Achieving HbA_{1c} <7%	10%	25%	36%
Body Weight (kg), Mean			
Baseline	99.1	94.9	95.2
Change at Week 30†	-0.8	-1.1	-1.6
Difference from placebo† (95% CI)		-0.3 [-1.1, 0.6]	-0.9 [-1.7, -0.0]
Fasting Plasma Glucose§ (mg/dL), Mean			
Baseline	194	180	178
Change at Week 30†	+6	-5	-11
Difference from placebo† (95% CI)		-11 [-25, 3]	-17 [-30, -3]

Table 6: Results of 30-Week and 16-Week Placebo-Controlled Trials of BYETTA Used in Combination with Oral Antidiabetic Agents (continued)

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
	In Combination With Metformin and a Sulfonylurea (30 Weeks)		
Intent-to-Treat Population (N)	247	245	241
HbA_{1c} (%), Mean			
Baseline	8.5	8.5	8.5
Change at Week 30†	+0.1	-0.7	-0.9
Difference from placebo† (95% CI)		-0.8 [-1.0, -0.6]‡	-1.0 [-1.2, -0.8]‡
Proportion Achieving HbA_{1c} <7%	8%	25%	31%
Body Weight (kg), Mean			
Baseline	99.1	96.9	98.4
Change at Week 30†	-0.9	-1.6	-1.6
Difference from placebo† (95% CI)		-0.7 [-1.2, -0.2]	-0.7 [-1.3, -0.2]
Fasting Plasma Glucose§ (mg/dL), Mean			
Baseline	181	182	178
Change at Week 30†	+13	-11	-12
Difference from placebo† (95% CI)		-24 [-33, -15]	-25 [-34, -16]
	In Combination With a Thiazolidinedione or a Thiazolidinedione plus Metformin (16 Weeks)		
Intent-to-Treat Population (N)	112	Dose not studied	121
HbA_{1c} (%), Mean			
Baseline	7.9	Dose not studied	7.9
Change at Week 16†	+0.1	Dose not studied	-0.7
Difference from placebo† (95% CI)		Dose not studied	-0.9 [-1.1, -0.7]‡
Proportion Achieving HbA_{1c} <7%	15%	Dose not studied	51%
Body Weight (kg), Mean			
Baseline	96.8	Dose not studied	97.5
Change at Week 16†	-0.0	Dose not studied	-1.5
Difference from placebo† (95% CI)		Dose not studied	-1.5 [-2.2, -0.7]
Fasting Serum Glucose§ (mg/dL), Mean			
Baseline	159	Dose not studied	164
Change at Week 16†	+4	Dose not studied	-21
Difference from placebo† (95% CI)		Dose not studied	-25 [-33, -16]

* BYETTA 5 mcg twice daily for 1 month followed by 10 mcg BID for 6 months for the 30-week trials or 10 mcg BID for 3 months in the 16-week trial before the morning and evening meals.

† Least squares means are adjusted for baseline HbA_{1c} strata or value, investigator site, baseline value of the dependent variable (if applicable), and background antihyperglycemic therapy (if applicable).

‡ p <0.01, treatment vs. placebo.

§ Measured using the hexokinase-based glucose method.

BID = twice daily.

HbA_{1c}

The addition of BYETTA to a regimen of metformin, a sulfonylurea, or both, resulted in statistically significant reductions from baseline in HbA_{1c} compared with patients receiving placebo added to these agents in the three controlled trials (Table 6).

In the 16-week trial of BYETTA add-on to thiazolidinediones, with or without metformin, BYETTA resulted in statistically significant reductions from baseline in HbA_{1c} compared with patients receiving placebo (Table 6).

Postprandial Glucose

Postprandial glucose was measured after a mixed meal tolerance test in 9.5% of patients participating in the 30-week add-on to metformin, add-on to sulfonylurea, and add-on to metformin in combination with sulfonylurea clinical trials. In this pooled subset of patients, BYETTA reduced postprandial plasma glucose concentrations in a dose-dependent manner. The mean (SD) change in 2-h postprandial glucose concentration following administration of BYETTA at Week 30 relative to baseline was -63 (65) mg/dL for 5 mcg BID (n=42), -71 (73) mg/dL for 10 mcg BID (n=52), and +11 (69) mg/dL for placebo BID (n=44).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BYETTA is supplied as a sterile solution for subcutaneous injection containing 250 mcg/mL exenatide.

The following packages are available:
5 mcg per dose, 60 doses, 1.2 mL prefilled pen, NDC 66780-210-07
10 mcg per dose, 60 doses, 2.4 mL prefilled pen, NDC 66780-212-01

16.2 Storage and Handling

Prior to first use, BYETTA must be stored refrigerated at 36°F to 46°F (2°C to 8°C). After first use, BYETTA can be kept at a temperature not to exceed 77°F (25°C). Do not freeze. Do not use BYETTA if it has been frozen. BYETTA should be protected from light. The pen should be discarded 30 days after first use, even if some drug remains in the pen. BYETTA should not be used past the expiration date. **BYETTA pens are not to be shared with other patients.**

17 PATIENT COUNSELING INFORMATION

Patients should be advised that BYETTA pens are never to be shared with another patient.

Patients should be informed of the potential risks and benefits of BYETTA and of alternative modes of therapy. Patients should also be fully informed about self-management practices,

including the importance of proper storage of BYETTA, injection technique, timing of dosage of BYETTA and concomitant oral drugs, adherence to meal planning, regular physical activity, periodic blood glucose monitoring and HbA_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

Patients should be advised to inform their physicians if they are pregnant or intend to become pregnant.

Each dose of BYETTA should be administered as a SC injection in the thigh, abdomen, or upper arm at any time within the 60-minute period **before** the morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). BYETTA **should not** be administered after a meal. If a dose is missed, the treatment regimen should be resumed as prescribed with the next scheduled dose.

The risk of hypoglycemia is increased when BYETTA is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea. The symptoms, treatment, and conditions that predispose to development of hypoglycemia should be explained to the patient. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating BYETTA therapy, particularly when concomitantly administered with a sulfonylurea *[see Warnings and Precautions (5.2)]*.

Patients should be advised that treatment with BYETTA may result in a reduction in appetite, food intake, and/or body weight, and that there is no need to modify the dosing regimen due to such effects. Treatment with BYETTA may also result in nausea, particularly upon initiation of therapy *[see Adverse Reactions (6)]*.

Patients should be informed that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue BYETTA and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

Patients treated with BYETTA should be informed of the potential risk for worsening renal function and informed about associated signs and symptoms of renal dysfunction, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.3)]*.

Patients should be informed that serious hypersensitivity reactions have been reported during postmarketing use of BYETTA. If symptoms of hypersensitivity reactions occur, patients must stop taking BYETTA and seek medical advice promptly *[see Warnings and Precautions (5.6)]*.

The patient should read the Medication Guide and the Pen User Manual before starting BYETTA therapy and review them each time the prescription is refilled. The patient should be instructed

on proper use and storage of the pen, emphasizing how and when to set up a new pen and noting that only one setup step is necessary at initial use. The patient should be advised not to share the pen and needles.

Patients should be informed that pen needles are not included with the pen and must be purchased separately. Patients should be advised which needle length and gauge should be used.

Manufactured for Amylin Pharmaceuticals, Inc., San Diego, CA 92121

Marketed by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company
1-800-868-1190

http://www.BYETTA.com

Literature Revised September 2010

 822016-AA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Victoza safely and effectively. See full prescribing information for Victoza.

Victoza® (liraglutide [rDNA origin] injection), solution for subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1).**
- **Victoza is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).**

INDICATIONS AND USAGE

Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Important Limitations of Use (1.1):

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (5.1).
- Has not been studied sufficiently in patients with a history of pancreatitis. Use caution (5.2).
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with insulin.

DOSAGE AND ADMINISTRATION

- Administer once daily at any time of day, independently of meals (2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2).
- The injection site and timing can be changed without dose adjustment (2).
- Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg (2).
- When initiating Victoza, consider reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia (2).

DOSAGE FORMS AND STRENGTHS

- Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL) (3).

CONTRAINDICATIONS

Do not use in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).

WARNINGS AND PRECAUTIONS

- Thyroid C-cell tumors in animals: Human relevance unknown. Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (5.1).
- Pancreatitis: In clinical trials, there were more cases of pancreatitis among Victoza-treated patients than among comparator-treated patients. If pancreatitis is suspected, Victoza and other potentially suspect drugs should be discontinued. Victoza should not be restarted if pancreatitis is confirmed. Use with caution in patients with a history of pancreatitis (5.2).
- Serious hypoglycemia: Can occur when Victoza is used with an insulin secretagogue (e.g. a sulfonylurea). Consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia (5.3).
- Macrovascular outcomes: There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug (5.4).

ADVERSE REACTIONS

- The most common adverse reactions, reported in ≥5% of patients treated with Victoza and more commonly than in patients treated with placebo, are: headache, nausea, diarrhea and anti-liraglutide antibody formation (6).
- Immunogenicity-related events, including urticaria, were more common among Victoza-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-484-2869 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Victoza delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use caution (7).

USE IN SPECIFIC POPULATIONS

- There are no data in patients below 18 years of age (8.4).
- Use with caution in patients with renal or hepatic impairment. Limited data (8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 1/2010

FULL PRESCRIBING INFORMATION: CONTENTS*
BOXED WARNING: RISK OF THYROID C-CELL TUMORS

*Sections or subsections omitted from the full prescribing information are not listed.

Exhibit B

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.

1 INDICATIONS AND USAGE

Victoza is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.1 Important Limitations of Use

- Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

- In clinical trials of Victoza, there were more cases of pancreatitis with Victoza than with comparators. Victoza has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza. Use with caution in patients with a history of pancreatitis.

- Victoza is not a substitute for insulin. Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

- The concurrent use of Victoza and insulin has not been studied.

2 DOSAGE AND ADMINISTRATION

Victoza can be administered once daily at any time of day, independently of meals, and can be injected subcutaneously in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment.

For all patients, Victoza should be initiated with a dose of 0.6 mg per day for one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg.

When initiating Victoza, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3) and Adverse Reactions (6)]*.

Exhibit B

Victoza solution should be inspected prior to each injection, and the solution should be used only if it is clear, colorless, and contains no particles.

3 DOSAGE FORMS AND STRENGTHS

Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

4 CONTRAINDICATIONS

Victoza is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice *[see Nonclinical Toxicology (13.1)]*. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications (4)]*.

In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment.

Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~ 1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated

with Victoza 1.2 mg, placebo and active control, respectively. Otherwise, Victoza did not produce consistent dose-dependent or time-dependent increases in serum calcitonin.

Patients with MTC usually have calcitonin values >50 ng/L. In Victoza clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza. The clinical significance of these findings is unknown.

Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

5.2 Pancreatitis

In clinical trials of Victoza, there were 7 cases of pancreatitis among Victoza-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza were reported as acute pancreatitis and two cases with Victoza were reported as chronic pancreatitis. In one case in a Victoza-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza treatment. After initiation of Victoza, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza should not be restarted. Use with caution in patients with a history of pancreatitis.

5.3 Use with Medications Known to Cause Hypoglycemia

Patients receiving Victoza in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza-treated patients and in no comparator-treated patients. Six of these 7 patients treated with Victoza were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues *[see Adverse Reactions (6.1)]*.

5.4 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Victoza was evaluated in a 52-week monotherapy trial and in four 26-week, add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza 1.2 mg daily, Victoza 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, patients were treated with Victoza 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza 1.2 mg, Victoza 1.8 mg or placebo *[see Clinical Studies (14)]*.

Withdrawals

The incidence of withdrawal due to adverse events was 7.8% for Victoza-treated patients and 3.4% for comparator-treated patients in the five controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza-treated patients and 0.5% of comparator-treated patients. The most common adverse reactions leading to withdrawal for Victoza-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

Tables 1 and 2 summarize the adverse events reported in ≥5% of Victoza-treated patients in the five controlled trials of 26 weeks duration or longer.

Table 1 Adverse events reported in ≥ 5% of Victoza-treated patients or ≥5% of glimepiride-treated patients: 52-week monotherapy trial

	All Victoza N = 497	Glimepiride N = 248
Adverse Event Term	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Upper Respiratory Tract Infection	9.5	5.6
Headache	9.1	9.3
Influenza	7.4	3.6
Urinary Tract Infection	6.0	4.0
Dizziness	5.8	5.2
Sinusitis	5.6	6.0
Nasopharyngitis	5.2	5.2
Back Pain	5.0	4.4
Hypertension	3.0	6.0

Table 2 Adverse events reported in ≥ 5% of Victoza-treated patients and occurring more frequently with Victoza compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Event Term	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza + Glimepiride N=695	Placebo + Glimepiride N=114	Rosiglitazone + Glimepiride N=231
Adverse Event Term	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
Add-on to Metformin + Glimepiride			
	Victoza 1.8+ Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Event Term	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
Add-on to Metformin + Rosiglitazone			
	All Victoza + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175	
Adverse Event Term	(%)	(%)	
Nausea	34.6	8.6	
Diarrhea	14.1	6.3	
Vomiting	12.4	2.9	
Decreased Appetite	9.3	1.1	
Anorexia	9.0	0.0	
Headache	8.2	4.6	
Constipation	5.1	1.1	
Fatigue	5.1	1.7	

Gastrointestinal adverse events

In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza-treated patients in the 26-week add-on combination therapy trials.

Among Victoza-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza treatment.

In clinical trials of Victoza, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

Injection site reactions

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza-treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza-treated patients discontinued due to injection site reactions.

Papillary thyroid carcinoma

In clinical trials of Victoza, there were 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

Hypoglycemia

In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza-treated patients (2.6 cases per 1000 patient-years) and in no comparator-treated patients. Six of these 7 patients treated with Victoza were also taking a sulfonylurea. One other patient was taking Victoza in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 3). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

Table 3 Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza** (N = 497)	**Glimepiride** (N = 248)	**None**
Patient not able to self-treat	0	0	-
Patient able to self-treat	9.7 (0.24)	25.0 (1.66)	-
Not classified	1.2 (0.03)	2.4 (0.04)	-
Add-on to Metformin	**Victoza + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
Patient not able to self-treat	0.1 (0.001)	0	0
Patient able to self-treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
Add-on to Glimepiride	**Victoza + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
Patient not able to self-treat	0.1 (0.003)	0	0
Patient able to self-treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
Add-on to Metformin + Rosiglitazone	**Victoza + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
Patient not able to self-treat	0	-	0
Patient able to self-treat	7.9 (0.49)	-	4.6 (0.15)
Not classified	0.6 (0.01)	-	1.1 (0.03)
Add-on to Metformin + Glimepiride	**Victoza + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
Patient not able to self-treat	2.2 (0.06)	0	0
Patient able to self-treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions (6.1)]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established.

Laboratory Tests
In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

7 DRUG INTERACTIONS

7.1 Oral Medications

Victoza causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, Victoza did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with Victoza.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.
There are no adequate and well-controlled studies of Victoza in pregnant women. Victoza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Liraglutide has been shown to be teratogenic in rats at or above 0.8 times the human systemic exposures resulting from the maximum recommended human dose (MRHD) of 1.8 mg/day based on plasma area under the time-concentration curve (AUC). Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rabbits at systemic exposures below human exposure at the MRHD based on plasma AUC.

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of

malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F_2 generation rats descended from liraglutide-treated rats compared to F_2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.3 Nursing Mothers

It is not known whether Victoza is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for liraglutide in animal studies, a decision should be made whether to discontinue nursing or to discontinue Victoza, taking into account the importance of the drug to the mother. In lactating rats, liraglutide was excreted unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

Safety and effectiveness of Victoza have not been established in pediatric patients. Victoza is not recommended for use in pediatric patients.

8.5 Geriatric Use

In the Victoza clinical trials, a total of 797 (20%) of the patients were 65 years of age and over and 113 (2.8%) were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

There is limited experience in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. Therefore, Victoza should be used with caution in this patient population. No dose adjustment of Victoza is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, Victoza should be used with caution in this patient population. No dose adjustment of Victoza is recommended for patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Gastroparesis

Victoza slows gastric emptying. Victoza has not been studied in patients with pre-existing gastroparesis.

10 OVERDOSAGE

In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

Victoza contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae,* has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

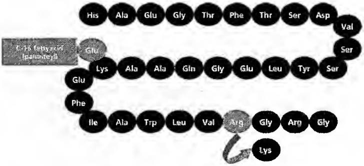


Figure 1 Structural Formula of liraglutide

Victoza is a clear, colorless solution. Each 1 mL of Victoza solution contains 6 mg of liraglutide. Each pre-filled pen contains a 3 mL solution of Victoza equivalent to 18 mg liraglutide (free-base, anhydrous) and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

12.2 Pharmacodynamics

Victoza's pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as Victoza lowered fasting, premeal and postprandial glucose throughout the day *[see Clinical Pharmacology (12.3)]*.

Fasting and postprandial glucose was measured before and up to 5 hours after a standardized meal after treatment to steady state with 0.6, 1.2 and 1.8 mg Victoza or placebo. Compared to placebo, the postprandial plasma glucose $AUC_{0\text{-}300min}$ was 35% lower after Victoza 1.2 mg and 38% lower after Victoza 1.8 mg.

Glucose-dependent insulin secretion

The effect of a single dose of 7.5 mcg/kg (~ 0.7 mg) Victoza on insulin secretion rates (ISR) was investigated in 10 patients with type 2 diabetes during graded glucose infusion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2).

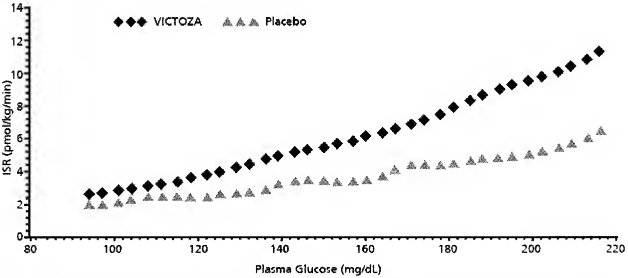


Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose Victoza 7.5 mcg/kg (~0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

Glucagon secretion

Victoza lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of Victoza 7.5 mcg/kg (~ 0.7 mg) did not impair glucagon response to low glucose concentrations.

Gastric emptying
Victoza causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Cardiac Electrophysiology (QTc)
The effect of Victoza on cardiac repolarization was tested in a QTc study. Victoza at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

12.3 Pharmacokinetics

Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (C_{max}) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h /mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, C_{max} and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg Victoza, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. $AUC_{0-\infty}$ was equivalent between upper arm and abdomen, and between upper arm and thigh. $AUC_{0-\infty}$ from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution - The mean apparent volume of distribution after subcutaneous administration of Victoza 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of Victoza is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%).

Metabolism - During the initial 24 hours following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Elimination - Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making Victoza suitable for once daily administration.

Specific Populations
Elderly - Age had no effect on the pharmacokinetics of Victoza based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age *[see Use in Specific Populations (8.5)].*

Gender - Based on the results of population pharmacokinetic analyses, females have 34% lower weight-adjusted clearance of Victoza compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Race and Ethnicity - Race and ethnicity had no effect on the pharmacokinetics of Victoza based on the results of population pharmacokinetic analyses that included Caucasian, Black, Asian and Hispanic/Non-Hispanic subjects.

Body Weight - Body weight significantly affects the pharmacokinetics of Victoza based on results of population pharmacokinetic analyses. The exposure of liraglutide decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of Victoza provided adequate systemic exposures over the body weight range of 40 – 160 kg evaluated in the clinical trials. Liraglutide was not studied in patients with body weight >160 kg.

Pediatric - Victoza has not been studied in pediatric patients *[see Use in Specific Populations (8.4)]*.

Renal Impairment - The single-dose pharmacokinetics of Victoza were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment - The single-dose pharmacokinetics of Victoza were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro assessment of drug-drug interactions

Victoza has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interactions

The drug-drug interaction studies were performed at steady state with Victoza 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to reach the maximum dose of 1.8 mg/day. Administration of the interacting drugs was timed so that C_{max} of Victoza (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Digoxin

A single dose of digoxin 1 mg was administered 7 hours after the dose of Victoza at steady state. The concomitant administration with Victoza resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximal concentration (T_{max}) was delayed from 1 h to 1.5 h.

Lisinopril

A single dose of lisinopril 20 mg was administered 5 minutes after the dose of Victoza at steady state. The co-administration with Victoza resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median T_{max} was delayed from 6 h to 8 h with Victoza.

Atorvastatin

Victoza did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of Victoza at steady state. Atorvastatin C_{max} was decreased by 38% and median T_{max} was delayed from 1 h to 3 h with Victoza.

Acetaminophen
Victoza did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of Victoza at steady state. Acetaminophen C_{max} was decreased by 31% and median T_{max} was delayed up to 15 minutes.
Griseofulvin
Victoza did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with Victoza at steady state. Griseofulvin C_{max} increased by 37% while median T_{max} did not change.

Oral Contraceptives
A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of Victoza at steady state. Victoza lowered ethinylestradiol and levonorgestrel C_{max} by 12% and 13%, respectively. There was no effect of Victoza on the overall exposure (AUC) of ethinylestradiol. Victoza increased the levonorgestrel $AUC_{0-\infty}$ by 18%. Victoza delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and could not be determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose *in vivo* micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11- times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

14 CLINICAL STUDIES

A total of 3978 patients with type 2 diabetes participated in 5 double-blind (one of these trials had an open-label active control insulin glargine arm), randomized, controlled clinical trials, one of 52 weeks duration and four of 26 weeks duration. These multinational trials were conducted to evaluate the glycemic efficacy and safety of Victoza in type 2 diabetes as monotherapy and in combination with one or two oral anti-diabetic medications. The 4 add-on combination therapy trials enrolled patients who were previously treated with anti-diabetic therapy, and approximately two-thirds of patients in the monotherapy trial also were previously treated with anti-diabetic therapy. In total, 272 (7%) of the 3978 patients in these 5 trials were new to anti-diabetic therapy. In these 5 clinical trials, patients ranged in age from 19-80 years old and 54% were men. Approximately 77% of patients were Caucasian, and 6% were Black. In the 2 trials where ethnicity was captured, 27% of patients were Hispanic/Latino and 73% were Non-Hispanic/Latino. In each of these trials, treatment with Victoza produced clinically and statistically significant improvements in hemoglobin A_{1c} and fasting plasma glucose (FPG) compared to placebo. Victoza did not have adverse effects on blood pressure.

All Victoza-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. Victoza 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance *[see Dosage and Administration (2)]*.

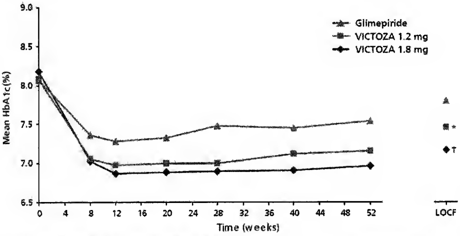
14.1 Monotherapy

In this 52-week trial, 746 patients were randomized to Victoza 1.2 mg, Victoza 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with Victoza 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA_{1c} compared to glimepiride (Table 4). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the Victoza 1.8 mg treatment group, 6.0% in the Victoza 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group.

Table 4 Results of a 52-week monotherapy trial[a]

	Victoza 1.8 mg	Victoza 1.2 mg	Glimepiride 8 mg
Intent-to-Treat Population (N)	246	251	248
HbA_{1c} (%) (Mean)			
Baseline	8.2	8.2	8.2
Change from baseline (adjusted mean)[b]	-1.1	-0.8	-0.5
Difference from glimepiride arm (adjusted mean)[b]	-0.6**	-0.3*	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.1)	
Patients (%) achieving A_{1c} <7%	51	43	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	172	168	172
Change from baseline (adjusted mean)[b]	-26	-15	-5
Difference from glimepiride arm (adjusted mean)[b]	-20**	-10*	
95% Confidence Interval	(-29, -12)	(-19, -1)	
Body Weight (kg) (Mean)			
Baseline	92.6	92.1	93.3
Change from baseline (adjusted mean)[b]	-2.5	-2.1	+1.1
Difference from glimepiride arm (adjusted mean)[b]	-3.6**	-3.2**	
95% Confidence Interval	(-4.3, -2.9)	(-3.9, -2.5)	

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
*p-value <0.05
**p-value <0.0001



*p-value = 0.0014 for VICTOZA 1.2 mg compared to glimepiride. †p-value < 0.0001 for VICTOZA 1.8 mg compared to glimepiride
P values derived from change from baseline ANCOVA model.

Figure 3 Mean HbA_{1c} for patients who completed the 52-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 52 (Monotherapy)

14.2 Combination Therapy

Add-on to Metformin

In this 26-week trial, 1091 patients were randomized to Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or glimepiride 4 mg (one-half of the maximal approved dose in the United States), all as add-on to metformin. Randomization occurred after a 6-week run-in period consisting of a 3-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day.

Treatment with Victoza 1.2 mg and 1.8 mg as add-on to metformin resulted in a significant mean HbA_{1c} reduction relative to placebo add-on to metformin and resulted in a similar mean HbA_{1c} reduction relative to glimepiride 4 mg add-on to metformin (Table 5). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the Victoza 1.8 mg + metformin treatment group, 3.3% in the Victoza 1.2 mg + metformin treatment group, 23.8% in the placebo + metformin treatment group, and 3.7% in the glimepiride + metformin treated group.

Table 5 Results of a 26-week trial of Victoza as add-on to metformin[a]

	Victoza 1.8 mg + Metformin	Victoza 1.2 mg + Metformin	Placebo + Metformin	Glimepiride 4 mg[†] + Metformin
Intent-to-Treat Population (N)	242	240	121	242
HbA_{1c} (%) (Mean)				
Baseline	8.4	8.3	8.4	8.4
Change from baseline (adjusted mean)[b]	-1.0	-1.0	+0.1	-1.0
Difference from placebo + metformin arm (adjusted mean)[b] 95% Confidence Interval	-1.1** (-1.3, -0.9)	-1.1** (-1.3, -0.9)		
Difference from glimepiride + metformin arm (adjusted mean)[b] 95% Confidence Interval	0.0 (-0.2, 0.2)	0.0 (-0.2, 0.2)		
Patients (%) achieving A_{1c} <7%	42	35	11	36
Fasting Plasma Glucose (mg/dL) (Mean)				
Baseline	181	179	182	180
Change from baseline (adjusted mean)[b]	-30	-30	+7	-24
Difference from placebo + metformin arm (adjusted mean)[b] 95% Confidence Interval	-38** (-48, -27)	-37** (-47, -26)		
Difference from glimepiride + metformin arm (adjusted mean)[b] 95% Confidence Interval	-7 (-16, 2)	-6 (-15, 3)		
Body Weight (kg) (Mean)				
Baseline	88.0	88.5	91.0	89.0
Change from baseline (adjusted mean)[b]	-2.8	-2.6	-1.5	+1.0
Difference from placebo + metformin arm (adjusted mean)[b] 95% Confidence Interval	-1.3* (-2.2, -0.4)	-1.1* (-2.0, -0.2)		
Difference from glimepiride + metformin arm (adjusted mean)[b] 95% Confidence Interval	-3.8** (-4.5, -3.0)	-3.5** (-4.3, -2.8)		

[a]Intent-to-treat population using last observation on study

[b]Least squares mean adjusted for baseline value

[†] For glimepiride, one-half of the maximal approved United States dose.

*p-value <0.05

**p-value <0.0001

Add-on to Sulfonylurea

In this 26-week trial, 1041 patients were randomized to Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased to 4 mg/day. The doses of glimepiride could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

Treatment with Victoza 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to glimepiride (Table 6). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the Victoza 1.8 mg + glimepiride

treatment group, 3.5% in the Victoza 1.2 mg + glimepiride treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the rosiglitazone + glimepiride treatment group.

Table 6 Results of a 26-week trial of Victoza as add-on to sulfonylurea[a]

	Victoza 1.8 mg + Glimepiride	Victoza 1.2 mg + Glimepiride	Placebo + Glimepiride	Rosiglitazone 4 mg[†] + Glimepiride
Intent-to-Treat Population (N)	234	228	114	231
HbA_{1c} (%) (Mean)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline (adjusted mean)[b]	-1.1	-1.1	+0.2	-0.4
Difference from placebo + glimepiride arm (adjusted mean)[b] 95% Confidence Interval	-1.4** (-1.6, -1.1)	-1.3** (-1.5, -1.1)		
Patients (%) achieving A_{1c} <7%	42	35	7	22
Fasting Plasma Glucose (mg/dL) (Mean)				
Baseline	174	177	171	179
Change from baseline (adjusted mean)[b]	-29	-28	+18	-16
Difference from placebo + glimepiride arm (adjusted mean)[b] 95% Confidence Interval	-47** (-58, -35)	-46** (-58, -35)		
Body Weight (kg) (Mean)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline (adjusted mean)[b]	-0.2	+0.3	-0.1	+2.1
Difference from placebo + glimepiride arm (adjusted mean)[b] 95% Confidence Interval	-0.1 (-0.9, 0.6)	0.4 (-0.4, 1.2)		

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
[†] For rosiglitazone, one-half of the maximal approved United States dose.
**p-value <0.0001

Add-on to Metformin and Sulfonylurea
In this 26-week trial, 581 patients were randomized to Victoza 1.8 mg, placebo, or insulin glargine, all as add-on to metformin and glimepiride. Randomization took place after a 6-week run-in period consisting of a 3-week forced metformin and glimepiride titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. After randomization, patients randomized to Victoza 1.8 mg underwent a 2 week period of titration with Victoza. During the trial, the Victoza and metformin doses were fixed, although glimepiride and insulin glargine doses could be adjusted. Patients titrated glargine twice-weekly during the first 8 weeks of treatment based on self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin glargine titration was left to the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18. Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of ≤100 mg/dL. Therefore, optimal titration of the insulin glargine dose was not achieved in most patients.

Treatment with Victoza as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo add-on to glimepiride and metformin (Table 7). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the Victoza 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

Table 7 Results of a 26-week trial of Victoza as add-on to metformin and sulfonylurea[a]

	Victoza 1.8 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride	Insulin glargine[†] + Metformin + Glimepiride
Intent-to-Treat Population (N)	230	114	232
HbA_{1c} (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline (adjusted mean)[b]	-1.3	-0.2	-1.1
Difference from placebo + metformin + glimepiride arm (adjusted mean)[b]	-1.1**		
95% Confidence Interval	(-1.3, -0.9)		
Patients (%) achieving A_{1c} <7%	53	15	46
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	165	170	164
Change from baseline (adjusted mean)[b]	-28	+10	-32
Difference from placebo + metformin + glimepiride arm (adjusted mean)[b]	-38**		
95% Confidence Interval	(-46,- 30)		
Body Weight (kg) (Mean)			
Baseline	85.8	85.4	85.2
Change from baseline (adjusted mean)[b]	-1.8	-0.4	1.6
Difference from placebo + metformin + glimepiride arm (adjusted mean)[b]	-1.4*		
95% Confidence Interval	(-2.1, -0.7)		

[a]Intent-to-treat population using last observation on study

[b]Least squares mean adjusted for baseline value

[†] For insulin glargine, optimal titration regimen was not achieved for 80% of patients.

*p-value <0.05

**p-value <0.0001

Add-on to Metformin and Thiazolidinedione

In this 26-week trial, 533 patients were randomized to Victoza 1.2 mg, Victoza 1.8 mg or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2000 mg). Patients underwent a 9 week run-in period (3-week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial.

Treatment with Victoza as add-on to metformin and rosiglitazone produced a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to metformin and rosiglitazone (Table 8). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the Victoza 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the Victoza 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

Table 8 Results of a 26-week trial of Victoza as add-on to metformin and thiazolidinedione[a]

	Victoza 1.8 mg + Metformin + Rosiglitazone	Victoza 1.2 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
Intent-to-Treat Population (N)	178	177	175
HbA_{1c} (%) (Mean)			
Baseline	8.6	8.5	8.4
Change from baseline (adjusted mean) [b]	-1.5	-1.5	-0.5
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b]	-0.9**	-0.9**	
95% Confidence Interval	(-1.1, -0.8)	(-1.1, -0.8)	
Patients (%) achieving A_{1c} <7%	54	57	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	185	181	179
Change from baseline (adjusted mean) [b]	-44	-40	-8
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b]	-36**	-32**	
95% Confidence Interval	(-44,- 27)	(-41, -23)	
Body Weight (kg) (Mean)			
Baseline	94.9	95.3	98.5
Change from baseline (adjusted mean) [b]	-2.0	-1.0	+0.6
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b]	-2.6**	-1.6**	
95% Confidence Interval	(-3.4, -1.8)	(-2.4, -1.0)	

[a]Intent-to-treat population using last observation on study

[b]Least squares mean adjusted for baseline value

**p-value <0.0001

16 HOW SUPPLIED/STORAGE HANDLING

16.1 How Supplied

Victoza is available in the following package sizes containing disposable, pre-filled, multi-dose pens. Each individual pen delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

2 x Victoza pen NDC 0169-4060-12
3 x Victoza pen NDC 0169-4060-13

Each Victoza pen is for use by a single patient. A Victoza pen should never be shared between patients, even if the needle is changed.

16.2 Recommended Storage

Prior to first use, Victoza should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C) (Table 9). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Victoza and do not use Victoza if it has been frozen.

After initial use of the Victoza pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Victoza should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Victoza pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy.

Table 9 Recommended Storage Conditions for the Victoza Pen

Prior to first use	After first use	
Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
Until expiration date	30 days	

17 PATIENT COUNSELING INFORMATION

17.1 Risk of Thyroid C-cell Tumors

Patients should be informed that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding is unknown. Patients should be counseled to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia or dyspnea) to their physician.

17.2 Pancreatitis

Patients should be informed that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to discontinue Victoza promptly, and to contact their physician, if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

17.3 Never Share a Victoza Pen Between Patients

Counsel patients that they should never share a Victoza pen with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.

17.4 Instructions

Patients should be informed of the potential risks and benefits of Victoza and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Patients should be advised that the most common side effects of Victoza are headache, nausea and diarrhea. Nausea is most common when first starting Victoza, but decreases over time in the majority of patients and does not typically require discontinuation of Victoza.

Physicians should instruct their patients to read the Patient Medication Guide before starting Victoza therapy and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

17.5 Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A_{1c} levels, with a goal of decreasing these levels towards the normal range. A_{1c} is especially useful for evaluating long-term glycemic control.

17.6 FDA-Approved Medication Guide

See separate leaflet.

Rx only

Date of Issue: January 2010
Version: 1

Victoza® is a registered trademark of Novo Nordisk A/S.

Victoza® is covered by US Patent Nos. 6,268,343, 6,458,924 and 7,235,627 and other patents pending.

Victoza® Pen is covered by US Patent Nos. 6,004,297, 6,235,004, 6,582,404 and other patents pending.

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Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exenatide on Glucose Control and Body Weight in Subjects With Type 2 Diabetes

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OBJECTIVE — In patients with type 2 diabetes, exenatide reduces A1C, postprandial and fasting glucose, and weight. In this study we investigated the effects of continuous exenatide administration from a long-acting release (LAR) formulation.

RESEARCH DESIGN AND METHODS — In this randomized, placebo-controlled phase 2 study, exenatide LAR (0.8 or 2.0 mg) was administered subcutaneously once weekly for 15 weeks to subjects with type 2 diabetes (n = 45) suboptimally controlled with metformin (60%) and/or diet and exercise (40%): 40% female, A1C (mean ± SD) 8.5 ± 1.2%, fasting plasma glucose 9.9 ± 2.3 mmol/l, weight 106 ± 20 kg, and diabetes duration 5 ± 4 years.

RESULTS — From baseline to week 15, exenatide LAR reduced mean ± SE A1C by −1.4 ± 0.3% (0.8 mg) and −1.7 ± 0.3% (2.0 mg), compared with +0.4 ± 0.3% with placebo LAR (P < 0.0001 for both). A1C of ≤7% was achieved by 36 and 86% of subjects receiving 0.8 and 2.0 mg exenatide LAR, respectively, compared with 0% of subjects receiving placebo LAR. Fasting plasma glucose was reduced by −2.4 ± 0.9 mmol/l (0.8 mg) and −2.2 ± 0.5 mmol/l (2.0 mg) compared with +1.0 ± 0.7 mmol/l with placebo LAR (P < 0.001 for both). Exenatide LAR reduced self-monitored postprandial hyperglycemia. Subjects receiving 2.0 mg exenatide LAR had body weight reductions (−3.8 ± 1.4 kg) (P < 0.05), whereas body weight was unchanged with both placebo LAR and the 0.8-mg dose. Mild nausea was the most frequent adverse event. No subjects treated with exenatide LAR withdrew from the study.

CONCLUSIONS — Exenatide LAR offers the potential of 24-h glycemic control and weight reduction with a novel once-weekly treatment for type 2 diabetes.

Diabetes Care 30:1487–1493, 2007

In the U.S., diabetes affects >21 million people, with combined direct and indirect costs of $132 billion annually (1). Treatment of this chronic, progressive disease often requires daily blood glucose monitoring and multiagent treatment regimens. However, despite the many medications available, the majority of people with type 2 diabetes are unable to maintain long-term glycemic control (2). The high prevalence of obesity in this population compounds this problem, as obesity is a risk factor for developing type 2 diabetes and worsens hyperglycemia and insulin resistance (3,4). Furthermore, use of many antihyperglycemic medications is associated with weight gain (5).

Incretin hormones, intestinally derived hormones that stimulate glucose-dependent insulin secretion in response to food intake, play an important role in glucose homeostasis (6). Glucagon-like peptide-1 (GLP-1) is an incretin hormone with multiple glucoregulatory actions, including enhancement of glucose-dependent insulin secretion, suppression of inappropriately elevated glucagon secretion, slowing of gastric emptying, and reduction of food intake and body weight (6–9). Postprandial secretion of GLP-1 is reduced in patients with type 2 diabetes (10), suggesting that the GLP-1 signaling pathway is an attractive therapeutic target. However, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-IV and has a relatively short half-life (~2 min) (6). The therapeutic potential of the GLP-1 pathway has led to the development of a class of compounds called incretin mimetics that share several glucoregulatory actions with GLP-1 but are resistant to dipeptidyl peptidase-IV degradation.

Exenatide, with a half-life of 2.4 h and clinical effects lasting up to 8 h, is the first clinically available incretin mimetic (10–16). Compared with GLP-1 in preclinical studies, exenatide has a 20- to 30-fold longer half-life and 5,500-fold greater potency in lowering plasma glucose (7,17). In placebo-controlled clinical trials in patients not achieving adequate glycemic control with metformin, a sulfonylurea, or a combination of both, 30 weeks of 10 μg subcutaneous exenatide twice daily (BID) resulted in statistically significant reductions in mean A1C, body weight, fasting plasma glucose, and postprandial plasma glucose excursions (18–20). Patients who continued in open-label extension studies for a total of 1.5 years (82 weeks) of BID exenatide treatment had sustained A1C reductions and progressive body weight reductions (21). In open-label comparator trials with insulin

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Received for publication 20 November 2006 and accepted in revised form 28 February 2007.

Published ahead of print at http://care.diabetesjournals.org on 12 March 2007. DOI: 10.2337/dc06-2375. Clinical trial reg. no. NCT00103935, clinicaltrials.gov

D.K., L.M., D.Z., M.F., and K.T. are employees and stockholders of Amylin Pharmaceuticals. P.K. and M.T. are employees and shareholders of Eli Lilly.

Abbreviations: BID, twice daily; GLP-1, glucagon-like peptide-1; ITT, intention to treat; LAR, long-acting release.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Exhibit C

glargine or 70/30 insulin aspart, exenatide treatment resulted in A1C reductions that were similar to those with insulin but with better postprandial glucose control and body weight reduction instead of weight gain (22,23). Mild-to-moderate nausea, which decreased over time, was the most common adverse event associated with exenatide in all of these trials.

A long-acting release (LAR) exenatide formulation for subcutaneous injection in patients with type 2 diabetes is under development to determine whether superior glycemic control can be achieved when exenatide is continuously present, compared with BID exenatide, which may not provide complete coverage after midday meals and overnight. In this report, we describe the effects of once-weekly subcutaneous administration of exenatide LAR for 15 weeks on glycemic parameters, weight, pharmacokinetics, safety, and tolerability in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS— Subjects enrolled in this study were 18–75 years of age, had type 2 diabetes treated for at least 3 months before screening with diet modification with exercise (i.e., taking no antidiabetes agent) and/or metformin, A1C of 7.1–11.0%, fasting plasma glucose <14.4 mmol/l, and BMI 25–45 kg/m^2. All of the subjects treated with metformin (total daily dose ranging from 500 to 2,550 mg) continued to receive the same dose throughout the study, with the exception of a subject in the 2.0 mg exenatide LAR arm who discontinued metformin and added insulin lispro and insulin glargine to her regimen 6 weeks after the last dose of study medication. Another change in antidiabetes treatment occurred when, after 9 weeks of placebo LAR, a subject initiated treatment with glimepiride (this subject subsequently withdrew from the study because of loss of glucose control). Subjects who had previously received exenatide treatment in a clinical trial were excluded from the study. Additionally, no subjects were treated with exenatide during the trial. A common clinical protocol was approved for each site by an institutional review board. All subjects provided written informed consent before participation, and the study was conducted in accordance with the principles described in the Declaration of Helsinki, including all amendments through the 1996 South Africa revision (24).

In this multicenter subject- and investigator-blinded phase 2 study, subjects (n = 45) were equally randomized to placebo LAR or 0.8 or 2.0 mg exenatide LAR. Blinded, randomized study medication kits with unique package numbers were prepared separately and shipped to each clinical site. The study-site pharmacist contacted an interactive voice response system to randomly assign subjects to a treatment group and find out which medication kit to dispense to each subject. Doses were targeted to result in concentrations previously found to be therapeutic with exenatide BID. Subjects underwent a 3-day lead-in of 5 μg exenatide or placebo subcutaneous BID to determine whether any subjects randomly assigned to exenatide LAR had an acute exenatide sensitivity. Then, once-weekly subcutaneous injections of 0.8 or 2.0 mg exenatide LAR or placebo LAR were administered at the study sites by study personnel for 15 weeks, with no changes in preexisting antidiabetes regimens. Subjects were monitored for adverse events and pharmacokinetics during a subsequent 12-week follow-up period during which time no study medications were administered. Generally, visits were conducted at weekly intervals. Study recruitment began 16 February 2005 and follow-up continued through 17 October 2005.

For self-monitored blood glucose profiles, subjects were given blood glucose meters and instructed to perform measurements by fingerstick at the fingertip. Preprandial glucose was measured 15 min before each meal, postprandial glucose was measured 1.5–2 h after each meal, and an additional glucose measurement was taken at 0300 h. Measurements were recorded on 3 separate days for both baseline and week 15.

Exenatide LAR consists of microspheres composed of exenatide and a poly(lactide-coglycolide) polymeric matrix. Poly(lactide-coglycolide) is a common biodegradable medical polymer with an extensive history of human use in absorbable sutures and extended-release pharmaceuticals. After injection, exenatide is slowly released from the microspheres through diffusion and erosion. Placebo LAR contained 0.5% ammonium sulfate instead of exenatide.

End points

Objectives of this study were to evaluate the safety, tolerability, and pharmacokinetics of exenatide LAR. Additional objectives were to evaluate pharmacodynamic (i.e., glucose), A1C, and weight effects of exenatide LAR. Safety was assessed by adverse events, clinical laboratory values, physical examination, and electrocardiograms. Adverse events, as reported by the subjects or noted by study-site staff incidentally or as a result of nondirected questioning, were categorized as mild if transient, requiring no special treatment, and not interfering with daily activities and as moderate if causing a low level of inconvenience, possibly interfering with daily activities, and ameliorated by simple therapeutic measures. An adverse event was categorized as severe if it interrupted a subject's usual daily activities and required systemic drug therapy or other treatment.

Laboratory values

Blood to measure plasma exenatide was drawn before study medication injection. Plasma exenatide concentrations were quantitated by a validated enzyme-linked immunosorbent assay (25) at LINCO Diagnostic Services (St. Charles, MO). A1C was quantitated by Quintiles Laboratories (Smyrna, GA) using high-performance liquid chromatography (26,27). Anti-exenatide antibodies were measured in a fashion similar to that described previously (25) at LINCO Diagnostic Services.

Statistical analysis

A sample size of 36 subjects was estimated to provide 95% CIs of ~65–115 and 170–290 pg/ml for the mean exenatide concentrations at steady state for 0.8 and 2.0 mg exenatide LAR, respectively. The intent-to-treat (ITT) population comprised all randomized subjects who received at least one injection of lead-in medication (n = 45), whereas the evaluable population consisted of subjects from the ITT population who completed the study procedures through week 15 in compliance with the protocol (n = 43). Descriptive statistics on demographics, safety, glycemic end points, and weight (i.e., mean values with either SE or SD, as appropriate) were provided for the ITT population. Descriptive statistics for self-monitored blood glucose measurements, which contained week 15 measurements, were performed for the evaluable population. The proportion of subjects achieving

Exhibit C

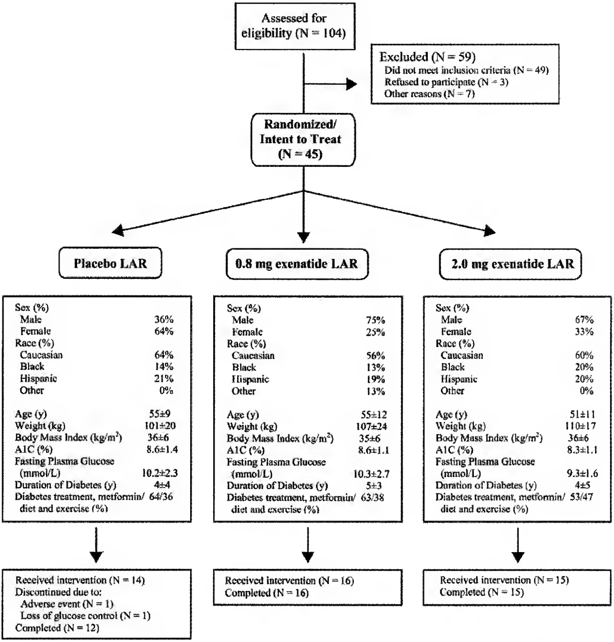

Figure 1— *Study flowchart. Disposition of patients throughout the study, with baseline demographics. Demographic data are means ± SD, except for sex, race, and diabetes treatment. Percentages may not add up to 100 because of rounding.*

A1C ≤7.0% also depended on week 15 measurements. The A1C target analysis was performed on the subset of evaluable patients with baseline A1C >7% ($n = 41$).

Plasma exenatide concentrations by treatment and time were provided for those subjects who received exenatide LAR and completed the study. Exenatide pharmacokinetics were analyzed by standard noncompartmental methods and summarized descriptively. Post hoc analyses were performed to compare the 0.8- and 2.0-mg exenatide LAR groups to the placebo LAR group with respect to the change from baseline for A1C, fasting plasma glucose, and body weight. Statistical significance was set at $P < 0.05$.

RESULTS

Subject demographics and disposition

Study subjects ($n = 45$) were 40% female and had the following mean ± SD baseline characteristics: A1C 8.5 ± 1.2%, fasting plasma glucose 9.9 ± 2.3 mmol/l, weight 106 ± 20 kg, and diabetes duration 5 ± 4 years. The different groups (Fig. 1) varied in their sex, with more women in the placebo LAR group and more men in the exenatide LAR groups, and glycemia, with lower A1C and fasting plasma glucose in the 2.0-mg exenatide LAR group. Most subjects in this study were receiving metformin ($n = 27$), whereas the remaining 18 subjects were

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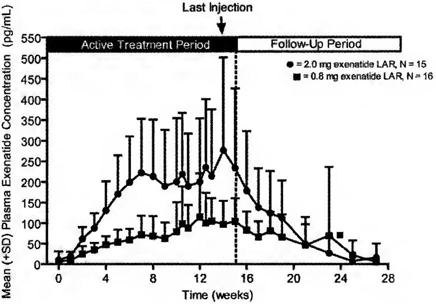

Figure 2— *Plasma exenatide concentrations (means ± SD) over time in subjects receiving exenatide LAR (n = 31). Note that the last injection was administered at week 14.*

treated with diet modification and exercise. Two subjects withdrew from the study, both from the placebo LAR group. One subject withdrew during the lead-in period because of an adverse event, and one subject withdrew during the treatment period because of loss of glucose control (Fig. 1).

Pharmacokinetics

With once-weekly exenatide LAR injections, mean plasma exenatide concentrations rose steadily. By week 2, treatment with 2.0 mg exenatide LAR reached 50 pg/ml, a concentration previously shown to significantly reduce plasma glucose (Fig. 2) (28). After ~6 weeks of treatment with 2.0 mg exenatide LAR, plasma exenatide concentrations were maintained at concentrations similar to the maximum concentration achieved with a single injection of 10 μg exenatide (steady-state concentration of 232 pg/ml with 2.0 mg exenatide LAR compared with 211 pg/ml after a single injection of 10 μg exenatide) (16). The steady-state concentration with 0.8 mg exenatide LAR was 111 pg/ml. After completion of the treatment phase at week 15, exenatide concentrations decreased steadily to below those considered to have a therapeutic effect by week 21.

Glycemic end points

Fasting plasma glucose was reduced rapidly, with significant mean ± SE changes from baseline to week 15 of −2.4 ± 0.9 and −2.2 ± 0.5 mmol/l for the 0.8- and 2.0-mg exenatide LAR groups, respectively, compared with +1.0 ± 0.7 mmol/l for the placebo LAR group ($P < 0.001$ for both 0.8 and 2.0 mg vs. placebo LAR) (Fig. 3*A*).

All three groups had similar self-monitored blood glucose profiles and mean average daily blood glucose concentrations at baseline (placebo LAR 11.3 mmol/l, 0.8 mg exenatide LAR 11.4 mmol/l, and 2.0 mg exenatide LAR 10.8 mmol/l) (Fig. 3*B*). By week 15, the mean average daily blood glucose concentration decreased for both LAR treatment groups (week 15 values 9.2 mmol/l [0.8 mg] and 8.3 mmol/l [2.0 mg]) and rose for the placebo LAR group (12.2 mmol/l). Preprandial and postprandial plasma glucose concentrations decreased for both exenatide LAR groups, with the magnitude of postprandial excursions decreased by as much as fourfold with 2.0 mg exenatide LAR compared with placebo LAR.

A1C was reduced at the first postexenatide LAR measurement (week 3) for both exenatide LAR groups and progressively decreased throughout the treatment period (Fig. 3*C*). At week 15, significant mean ± SE A1C changes from baseline of −1.4 ± 0.3 and −1.7 ± 0.3% were observed for the 0.8- and 2.0-mg exenatide LAR groups, respectively, compared with +0.4 ± 0.3% for the placebo LAR group ($P < 0.0001$ for both 0.8 and 2.0 mg vs. placebo LAR), resulting in mean A1C values of 7.2 and 6.6% in the 0.8- and 2.0-mg exenatide LAR groups, respectively, compared with 9.0% for the placebo LAR group. Of evaluable subjects with baseline A1C >7% ($n = 41$), 86% in the 2.0-mg group and 36% of subjects in the 0.8-mg group achieved an A1C of ≤7% at week 15, compared with 0% of subjects in the placebo LAR group.

Weight

Body weight decreased progressively in the 2.0-mg exenatide LAR group, with a significant mean ± SE change from baseline at week 15 of −3.8 ± 1.4 kg (3.5% of total baseline body weight) (Fig. 3*D*) ($P < 0.05$ for 2.0 mg exenatide LAR vs. placebo LAR). Body weight was unchanged for the 0.8-mg exenatide LAR and placebo LAR groups.

Safety and tolerability

All adverse events were mild to moderate in intensity, except for one severe adverse event of urticaria and pruritus, which was considered to be related to shellfish ingestion not to exenatide treatment. Nausea was the most frequently reported adverse event among exenatide LAR-treated subjects (exenatide LAR 0.8 mg 19% and 2.0 mg 27% vs. placebo LAR 15%), followed by gastroenteritis (exenatide LAR 0.8 mg 19% and 2.0 mg 13% vs. placebo LAR 0%), and hypoglycemia (exenatide LAR 0.8 mg 25% and 2.0 mg 0% vs. placebo

Exhibit C

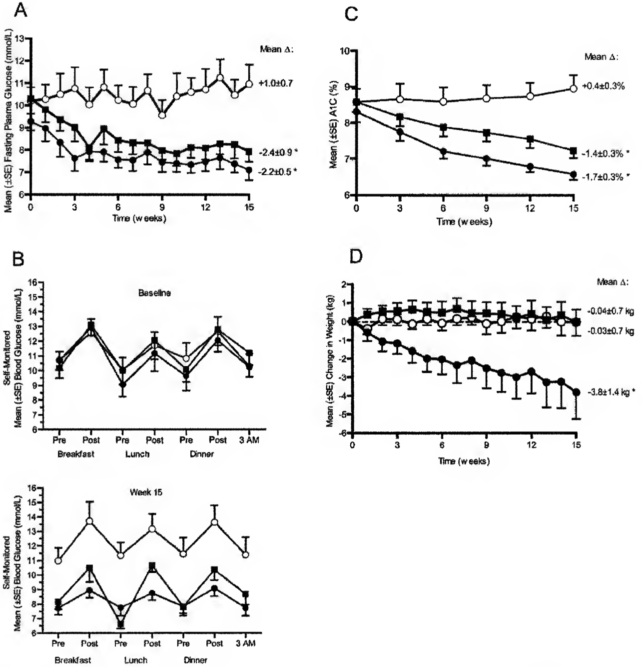

Figure 3— *Glycemic and weight parameters. Unless otherwise indicated:* O, *placebo LAR,* n = *14;* ■, *0.8 mg exenatide LAR,* n = *16;* ●, *2.0 mg exenatide LAR,* n = *15. *Statistically significant results:* P < *0.05 compared with placebo LAR (A, C, and D). A: Fasting plasma glucose concentrations over time (ITT,* n = *45; mean ± SE). B: Self-monitored blood glucose concentration profiles at baseline and week 15 (evaluable,* n = *43; mean ± SE).* O, *placebo LAR,* n = *12;* ■, *0.8 mg exenatide LAR,* n = *16;* ●, *2.0 mg exenatide LAR,* n = *15. C: A1C (%) over time (ITT,* n = *45; mean ± SE). D: Change in body weight from baseline over time (ITT,* n = *45; mean ± SE).*

LAR 0%). All episodes of nausea were mild, with no reports of vomiting. Hypoglycemic episodes, only one of which was confirmed with a blood glucose concentration (3.1 mmol/l), were mild in intensity and were not related to the dose of exenatide LAR (as all occurred in the 0.8-mg group). Injection site bruising occurred more frequently in exenatide LAR-treated patients (exenatide LAR 0.8 mg 13% and 2.0 mg 7% vs. placebo LAR 0%).

There were no withdrawals because of adverse events during exenatide LAR treatment. There were no clinically significant abnormal hematologic, chemistry, or urinalysis values reported during the study. Further, there were no clinically significant abnormalities in vital signs and electrocardiogram interpretations.

At week 15, 67% of subjects in the exenatide LAR treatment groups were positive for anti-exenatide antibodies. Individual subject profiles did not reveal a

Exhibit C

clear association between antibody response and effects on safety or efficacy.

CONCLUSIONS — Development of an exenatide formulation with once-weekly dosing that reduces A1C and weight could provide patients and clinicians with a novel tool with which to treat type 2 diabetes. In this study, once-weekly exenatide LAR for 15 weeks had multiple metabolic effects, including significant reductions of A1C, weight, and fasting glucose and marked reduction of self-monitored postprandial glucose. Treatment with 2.0 mg exenatide LAR but not with 0.8 mg reduced body weight, indicating that higher exenatide concentrations are required for effects on weight. This dose dependence in weight effects is in keeping with the observed results of 30-week placebo-controlled studies of exenatide on a background of metformin or sulfonylurea treatment (18,19). Likewise, the magnitude of postprandial glucose excursions decreased as much as fourfold with 2.0 mg exenatide LAR (compared with placebo LAR), which may account for the greater magnitude of A1C reduction with the 2.0-mg dose.

A single dose of the BID formulation of exenatide has a half-life of 2.4 h after subcutaneous injection, predominantly because of renal clearance, and is administered before the two main meals of the day, ≥6 hours apart (16). Improvements in postprandial glycemia with exenatide BID have been most pronounced at breakfast and dinner, the meals before which exenatide is typically given, with some residual beneficial effects after lunch and during fasting. In contrast, treatment with exenatide LAR provides 24-h exposure to therapeutic exenatide concentrations. This continuous exposure may account for the reduction in fasting glucose observed with 15 weeks of exenatide LAR being fourfold greater than that reported in 30-week studies with 10 μg exenatide BID (18–20). In addition, exenatide LAR provides postprandial glycemic control with all meals. This combination of daylong fasting and postprandial effects may explain why the A1C reduction was approximately twice as large with 2.0 mg exenatide LAR compared with exenatide BID and why the majority of subjects (86%) achieved target A1C values of ≤7%. Similarly, it is possible that the twofold greater weight reduction could reflect effects on food intake throughout the day with 2.0 mg exenatide LAR, as opposed to presumably only at breakfast and dinner with exenatide BID.

Continuous GLP-1 infusion improves glycemic control, weight, insulin sensitivity, and β-cell function (8,29). However, whereas GLP-1, with a half-life of <2 min (6), is administered as a continuous infusion, exenatide LAR, with a median half-life of 2 weeks (data on file; Amylin Pharmaceuticals, San Diego, CA), can be administered as a once-weekly subcutaneous injection. Exenatide acts in a glucose-dependent manner, affecting insulin and glucagon secretion during hyperglycemia but not euglycemia or hypoglycemia. Therefore, continuous exenatide concentrations can potentially improve glycemic control and other metabolic measures without increasing the risk of clinically significant hypoglycemia.

Exenatide LAR was well tolerated, with almost exclusively mild-to-moderate adverse events. The relatively mild nausea profile with exenatide LAR compared with that observed with exenatide BID (18–20) may be due to the more gradual increase in plasma exenatide concentrations upon initiation of treatment. In support of this hypothesis, stepwise introduction of exenatide has been shown to reduce the incidence of nausea by approximately half (30). The formation of anti-exenatide antibodies with exenatide LAR treatment was not predictive of end point response or adverse safety outcome, consistent with exenatide BID studies (18–20). Longer-term studies are needed to examine the safety profile of exenatide LAR. Thus far, exenatide BID has been on the market for ~2 years and has been studied in clinical trials of up to 3 years in duration (31) without significant changes to its safety profile.

Although these findings are encouraging, the relatively modest size (45 subjects) and short duration (15 weeks) of the study and administration of exenatide LAR by study staff must all be considered when interpreting these findings. The reductions in A1C and weight did not appear to plateau by week 15, so the full potential for and sustainability of glycemic improvement and weight reduction were not determined by this study. Additionally, the administration of injections by study staff at study sites ensured high compliance and a uniform injection technique, which may not reflect real-world clinical use.

In this early study, the data suggest that a convenient, once-weekly exenatide formulation shows promise in the treatment of type 2 diabetes. The combined potential benefits of improved glycemic control and reduced weight in a novel once-weekly treatment regimen for patients with type 2 diabetes merits longer-term large-scale studies to gain further insight into treatment with exenatide LAR.

Acknowledgments— This work was supported by Amylin Pharmaceuticals, San Diego, CA, Eli Lilly and Company, Indianapolis, IN, and Alkermes, Cambridge, MA.

The authors thank the exenatide LAR clinical team for their assistance in the conduct, reporting, and quality control of the study and development of the manuscript; the investigators Andrew Ahmann, Bruce Berwald, Eric Klein, Sam D. Miller, John Pullman, and Richard Weinstein and the study site staffs for conducting the study; the study subjects for their participation; and Susanna Mac for writing of the manuscript. We thank Alkermes for leading the development of and for manufacturing the long-acting release formulation of exenatide.

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Exhibit C